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Lung Involvement in Neuroblastoma: Incidence and Characteristics

Fiona Cowie, MBBS, MD,[1]* Robin Corbett, MBBS, MD,[2] and C. Ross Pinkerton, MBBS, MD[3]

The presence of lung metastases in neuroblastoma often leads to doubt about the diagnosis due to rarity of disease at this site. To determine more precisely the incidence and nature of pulmonary disease in neuroblastoma the data base of the European Neuroblastoma Study Group (ENSG) was examined. Information was obtained about 35/746 stage IV patients (and 1 patient who was registered as having stage II disease) documented to have pulmonary disease at presentation. Of these 5 were registered with pleural effusions, 18 pleural infiltrations, and 13 intrapulmonary lesions. Review of these cases, however, suggested that only 9 patients (1.2%; 95% exact confidence interval 0.42–1.99%, binomial distribution) had disease consistent with secondary neuroblastoma in lung or pleura. There was no correlation with clinical features, age, sex, or other disease sites, and outcome was uniformly poor. Med. Pediatr. Oncol. 28:429–432, 1997.

Key words: neuroblastoma; pulmonary disease; metastases; incidence

INTRODUCTION

While it is recognized that the incidence of pulmonary involvement in neuroblastoma is rare, the true incidence is unknown. Following the presentation of two patients with multiple lung secondaries the data held in the European Neuroblastoma Study Group (ENSG) data base were examined in order to establish the incidence of pulmonary or pleural involvement in neuroblastoma.

Most published data are derived from autopsies and all are relatively small single center reviews. At death the frequency of lung metastases is described as between 23 and 57% [1–3]. No previous attempt has been made to determine the incidence at presentation in a large multicenter series of patients. This retrospective study aims to establish the incidence of pleural or pulmonary metastases at presentation in stage IV neuroblastoma.

PATIENTS AND METHODS

Between 1982 and 1993 almost all patients with neuroblastoma in the United Kingdom and many of those in Europe were registered with the ENSG. Registration documents included details of the center at which the patient was treated, demographic information (age, sex, and stage and sites of disease), treatment used (either on or off a formal study protocol), and follow-up information (collected on an annual basis) with sites of relapse and cause of death if appropriate.

The records of the first 1,245 cases registered with the ENSG were reviewed (this covers the first 10 years of the data base) and details recorded about those patients with lung or pleural involvement (including those with pleural effusion) at presentation. These records consisted of the original forms completed and returned (for each child) by the responsible physician. The referring centers were then either visited or contacted by post for further specific information about each of these patients. The consultant's consent was obtained in all cases. This allowed an informed retrospective decision on the nature of recorded pulmonary or pleural disease.

RESULTS

Patients (1,245) were registered between March 1982 and July 1992; the data base was closed in 1993. The demographic data for the first 1,245 patients are as follows: 54.1% male, 59.9% Evans stage IV, and median age 2.2 years (range 0.0–24.1 years). While most patients were registered with both Evans stage and International Neuroblastoma Staging System after 1989, before this Evans stage alone was used.

From completed registration documents for those 746 patients registered with stage IV disease, 82.3% (614) had an abdominal primary, 5.36% of tumors were thoracoabdominal, 4.3% were thoracic, 4% unknown, and the

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[1]Beatson Oncology Center, Western Infirmary, Glasgow, United Kingdom; [2]Paediatric Department, Christchurch Hospital, New Zealand; [3]Paediatric Department, Royal Marsden Hospital, Sutton Surrey, United Kingdom.

*Correspondence to: Dr. Fiona Cowie, Beatson Oncology Center, Western Infirmary, Glasgow G11 6NT, United Kingdom.

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remaining 4% were cervical, pelvic, or multiple. Metastatic sites commonly involved in these patients included bone marrow (582 patients), bone metastases (512 patients), lymph nodes (416 patients), and liver (158 patients).

Further information was obtained on 36 patients registered with pleural effusion, pulmonary or pleural disease at presentation. One patient was registered as stage II neuroblastoma with pulmonary metastases, however, she was considered a stage IV patient in this study.

Pulmonary Disease

Thirteen of 36 patients had pulmonary disease at presentation. Six patients had direct extension of the primary tumor into lung. Two patients had lung disease reported as more consistent with consolidation than metastases [on chest X-ray (CXR) or computerized tomographic (CT) scan]. One had a single pulmonary lesion and four had multiple bilateral lesions which were thought to represent metastases by the reporting radiologist. One of these patients also had pleural metastases.

Pleural Disease

Eighteen of 36 patients had pleural disease at diagnosis. Eight had a pleural effusion rather than any evidence of pleural disease, two had both extension of the primary tumor and an effusion, two had extension of the primary site into pleura, one had a ''pleural reaction'' due to extensive intra-abdominal disease, and one had extension from involved lymph nodes. Four patients had true pleural metastases; one of these was only recognized following postmortem examination. This patient died 12 days after the diagnosis of neuroblastoma had been made and did not receive any treatment.

Pleural Effusion

Five patients were registered with a pleural effusion at diagnosis. In all patients who were registered as having a pleural effusion at presentation this was evident on CXR and at least three had pleural fluid aspirated. In these three recorded cases, the pleural aspirate was positive for malignant cells.

There were 11 other cases which were not specifically registered as having a pleural effusion, but in whom the registration document suggested intrathoracic disease. On review of their case records, intrathoracic disease consisted of an effusion plus either pulmonary consolidation or direct extension from a disease site (primary or lymph node spread). In view of the considerable difficulty in determining if a pleural effusion was malignant or reactive (in the absence of cytology), and the uncertainty about completeness of registration of all cases with a pleural effusion, pleural effusion as a site of pulmonary or pleural disease was not included.

In summary, from a group of 1,245 patients with neuroblastoma, 4 had pulmonary disease, 4 had pleural disease, and 1 had both pleural and pulmonary disease at diagnosis. Thus, 0.7% [95% confidence interval (CI) 0.24–1.16%] of all patients presenting with neuroblastoma had pleural or pulmonary disease as recognized on CXR or CT scan.

Table I displays information on those few patients who had either pulmonary or pleural disease at presentation. In most cases, disease was demonstrated on either CXR or CT scan; in one patient (who did not have a CT scan) pleural disease was only recognized on postmortem examination. In at least five patients (four of these had pleural disease) the CXR at diagnosis was thought to be normal. In three cases pulmonary disease was evident on CXR; for the remaining case (also pulmonary) it is not clear whether or not plain CXR was normal.

Case 613 was initially registered as stage II with an adrenal primary. The lung was felt to be abnormal at the time of initial surgery and pulmonary metastases were subsequently seen on CT images of the thorax. No attempt was made to obtain tissue for histology to confirm pulmonary involvement with neuroblastoma in a patient with no other metastatic site. Chemotherapy and further surgery followed, but the child only achieved a partial response and later developed pre-B acute lymphoblastic leukemia.

Case 1174 was recognized to have both pleural and pulmonary disease at presentation following a CT scan (CXR only suggested pulmonary disease).

DISCUSSION

The incidence of pulmonary involvement at diagnosis is thought to be low with an estimate of 4% in children over 1 year old with stage IV neuroblastoma [4]. This abstract cites 15 of 363 children with lung involvement at presentation; no comment is made regarding staging investigations used. However, it suggests (data not given) that in those children tested, lung disease correlates with N myc amplification. Pulmonary neuroblastoma has also been reported in two case reports where disseminated pulmonary disease developed following autologous bone marrow transplant (ABMT) for stage IV disease (both with initial bone marrow involvement) [5,6]; in one case the infused bone marrow had been purged.

One problem in attempting to ascertain the incidence of pulmonary involvement is the distinction between ex-

TABLE I. Details on Patients With Pulmonary or Pleural Disease at Presentation*

ENSG No.	Age (years) /sex	Primary disease site	Metastatic sites	''Confirmation'' of pulmonary/pleural disease	Outcome
189	1.5/M	Left adrenal	Bone marrow, bone, liver, ↑VMA, lung	CT scan: multiple bilateral pulmonary deposits; CXR normal	Died of disease 1 year after diagnosis
238	15/M	Sympathetic chain	Bone, skin, lymph nodes, ↑VMA, pleura, bone marrow	CT scan: 2 pleural metastases; CXR normal	Died of neutropenic sepsis during autograft
597	3/F	Left adrenal	Bone marrow, bone, liver, pleura	Postmortem: mass in pleura adjacent to a normal vertebra; CXR normal	Died 21 days after presentation with disease
613	2/M	Left adrenal	Lung	CT: multiple pulmonary metastases	Died 5 years after initial diagnosis
664	2/F	Right adrenal	Lymph nodes, liver, ↑VMA, lung	CXR: multiple bilateral pulmonary metastases	Died of disease 6 months after diagnosis
852	3/F	Right adrenal	Bone, bone marrow, lymph nodes, pleura	CT: single pleural deposit; CXR normal	Died of disease 2 years after diagnosis
1147	1.5/F	Right adrenal	Bone, bone marrow, lung	CXR: single discrete pulmonary mass	Died of disseminated neuroblastoma
1174	1.25/M	Right adrenal	Lymph nodes, liver, ↑VMA, lung, pleura	Bilateral pulmonary and pleural metastases on CXR, CT scan, and mIBG scan	Died of disseminated disease 2 months after diagnosis
1205	3/F	Sympathetic chain	Bone, bone marrow, ↑VMA, pleura	CT: pleural mass, separate from primary, confirmed on biopsy; CXR normal	Unknown

*VMA, vanillyl mandelic acid; mIBG, meta iodobenzylguanidine.

tension of a primary tumor into the thorax and discrete pulmonary metastases. If the lesion is not biopsied distinction between infection or consolidation and metastases may be difficult or impossible. An additional factor is the use of chest CT scanning. Of the cases presented here which were positive for pleural or pulmonary metastases, 5/9 were known to have a normal CXR. While a chest CT is recommended by the ENSG as part of the initial staging investigations, it is not mandatory. It is likely that the detected incidence of lung or pleural metastases at presentation is an underestimate—both in this study and in clinical practice.

Most cases in this study had no histological verification of involvement of the pleura or lungs with neuroblastoma. This was undertaken in only 2/9 cases. This raises the question of accuracy when diagnosing the lung or pleura as a metastatic site. In many cases, such a decision was made based upon clinical and radiological evidence. Alternatives to metastatic disease need to be considered in all cases. These include consolidation or collapse due to infection, staphylococcal abscesses, and direct extension or infiltration of the primary into lung parenchyma or pleura rather than discrete metastases.

In general, children with stage IV neuroblastoma will only have one disease site biopsied; other sites of disease will be investigated by non-invasive techniques [radiology, meta iodobenzylguanidine (mIBG), and bone marrow examination]. In most cases, only limited information is available about the molecular status of a tumor (e.g., CD44, nMYC, and 1p deletion) which may form part of a research project, or only be available after treatment has been initiated. The details held in the ENSG data base included results of mIBG, CXR, and urinary VMA estimation on all patients, however, in many patients this was not further qualified. It is therefore impossible in this type of retrospective study to determine the complete extent of metastatic burden, only which sites were involved.

The presence of a pleural effusion was recorded on the ENSG registration forms in a few cases. This was qualified with the statement ''cytology positive'' or ''negative'' in some. Pleural effusion was underreported (based upon findings when a limited sample of hospital case records was reviewed); this may have been on the assumption that the effusion was a reactive feature or related to an infectious process. In view of this, it was decided not to include pleural effusion in this analysis, recognizing that in some cases it may have represented a truly involved disease site.

Thus, with the current commonly used investigation techniques (CXR and CT scans), pulmonary or pleural metastases are rarely recognized in neuroblastoma (~1% at presentation). The lung and pleura do not appear to be an isolated site of metastatic disease. The value of diagnosing pulmonary or pleural metastases on CT scan or CXR is questionable in the face of widely metastatic disease as it will not alter staging, treatment, or outcome. CT scan is (as might be expected) more sensitive than CXR, but it is not performed routinely.

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